

**A STUDY OF POLYCYTHEMIA VERA WITH SPLENOMEGALY,
WITH A REPORT OF TWO CASES, AND A DISCUSSION OF
THE TREATMENT BY THE ROENTGEN RAYS.***

By E. P. PENDERGRASS, M.D.,

ASSISTANT ROENTGENOLOGIST TO THE UNIVERSITY HOSPITAL, PHILADELPHIA.

Definition. Polycythemia with splenomegaly is a disease in which there is an increase in the total number of red blood corpuscles and in the total volume of blood, usually associated with cyanosis and general weakness. This disease was first described by Vaquez in 1892, and Osler, in 1902, gave a more complete study of polycythemia, establishing it as a new clinical entity.

Etiology. The cause of the disease is unknown, but there are a number of theories as to its etiology.

Polycythemia vera occurs more frequently in men than in women, and usually occurs between the ages of thirty-five to fifty-five years. It is an insidious disease, lasting from eight months to ten years, the patient then dying from cerebral hemorrhage or from some intercurrent disease. Benet⁷ believes that polycythemia is due to a decreased capacity of the hemoglobin for oxygen. This being primary, an increase in the red cells takes place. This theory is supported by the compensatory polycythemia, which occurs in high altitudes where there is a lack of oxygen and the fact that inhalation of oxygen decreases the red cells. Lommel⁸ thinks the primary cause is stasis of the blood. Lefas, Rendu, Widal¹⁰ and others think the disease a primary splenic tuberculosis. Neehanin¹¹ believes heredity may play some part in the etiology of polycythemia. He tells of a case of a female student with a slight polycythemia, whose mother and sister each had cyanosis and an enlarged spleen. De Chapelle¹⁴ called attention to the history of injury as a cause of polycythemia. Three of Osler's cases laid great stress on some injury, a strain in 2 cases and the kick of a horse in the third. One case reported below had an injury to his neck in early childhood, and Stengel at that time thought that this might have played some part in the cause of the polycythemia.

The immediate causes of polycythemia have been variously ascribed to either a diminished destruction of the red cells, due to an increased resistance of the red cells to the hemolytic anaboceptor, as was seen in one case reported by Pichard,¹³ or, on the other hand, an increased production of red cells.⁶

Symptoms. Cyanosis, general weakness, enlargement of the spleen, headache and constipation are the prominent symptoms of which the patient complains. In polycythemia the patients are particularly prone to hemorrhages.

* Read before the Pathological Society of Philadelphia, May 26, 1920.

Summary of the Blood Findings. The total amount of blood is increased. This is easily determined by the method of Haldane and Smith.²⁷

Red Blood Cells. The number is greatly increased, usually averaging about 8,000,000. In one case reported 14,180,000 red cells were found by J. Hnatek.²⁸

Normoblasts. Occasionally normoblasts are found. There may be some anisocytosis and poikilocytosis. The viscosity of the blood is increased in some cases to four or five times the normal.

Leukocytes. They run parallel, with the reds usually. There is a tendency to an increase in the percentage of the polymorphonuclear leukocytes.

Hemoglobin. This is markedly increased but not parallel to the increase of red cells.

Color Index. Less than 1.

Specific Gravity. 1050 to 1065.

The iron, lecithin and phosphoric acid contents of the blood are increased and the salts of the blood are normal.

Blood Serum. This has a low specific gravity, with a low protein content.

In some cases there is associated with the polycythemia a leukemic manifestation. In looking over the literature five cases have been reported in which myelocytes were found in the differential blood examination. Chief among these is the case reported by Blumenthal² in which he found the following blood picture: Red cells 11,450,000; white cells, 16,300; Hb., 110 per cent.

The differential count showed 45 per cent. myelocytes.

Pathological Anatomy. In reviewing the cases of polycythemia vera with splenomegaly and cyanosis there are only a few out of the total number reported that have autopsy findings of the bone-marrow included in the reports. Some of these autopsies were evidently carried out carelessly because the observations at the autopsy table were not supplemented by the laboratory examinations of the bone-marrow, spleen, etc.

The pathologic findings in the cases reported do not show any conformity in pathology, excepting the increase of blood in the bloodvessels of all organs. There is a hyperplasia of the erythroblastic and to a slight degree of the leukoblastic tissues of the bone-marrow. Red marrow is found in many places where yellow marrow is normally found. Westenhöpper¹⁵ compares the bone-marrow of polycythemia vera to that of a child. There are an excessive number of eosinophiles and bone-marrow mast cells.

Spleen. The spleen is decidedly increased in size and filled with blood. There is a mild hyperplasia of all the connective-tissue elements, and Hirschfeld¹² found a slight myeloid transformation of the splenic pulp with an increase of the leukocytes and normoblasts. In some cases there are infarcts, in others tuberculosis of

the spleen and in one case of Senator's⁶ he found two areas of gummatous masses, although an antemortem blood examination showed the blood Wassermann negative.

Lymph Nodes. There is a lymphadenoid metaplasia, with an increase of the blood in these structures.

Autopsy reports collected from the literature:

Case of Wakasugi, K.¹ Bone-marrow. Medulla of sternum and ribs; dark red. Upper femur: Dark red; lower femur yellow.

Microscopic examination: All cells were found, *i. e.*, myelocytes, nucleated reds, eosinophilic and neutrophilic leukocytes and a few lymphocytes.

Spleen: Normal. No increased phagocytosis.

Conclusion: Hypertrophy of erythroblastic tissue of the bone-marrow.

Case of Rendu and Vidal¹⁰ de Montard, Martin et Lafas:⁹ Conclusion: Fibrocascations; tuberculosis of the spleen.

Case of Cabot, R. C.:³ Red cells, 10,460,000; leukocytes, 20,000; hemoglobin, 120 per cent.; passive congestion of all organs; nothing clearly seen in the spleen.

Case of Saunby and Russell:²⁵ Red cells, 9,000,000; spleen enlarged, syphilis thought to be the cause; spleen of normal consistency; heart, hypertrophy of left ventricle.

Case of Türk:²⁶ Red cells, 7,500,000; hemoglobin, 112 per cent.; congestion of all organs; spleen congested; chronic tumefaction with anemic infarct; kidney, parenchymatous nephritis; apoplectic stroke the cause of death.

Case of Türk:²⁶ Red cells, 8,024,070; white cells, 26,300; occasional myelocytes; jaundice; enlarged liver, hepatic cirrhosis; enlarged spleen, chronic tumefaction of the spleen; bones, diaphyses uniformly red.

Case of Bauer:²⁷ Bone-marrow, no alterations; spleen, large; no other changes.

Case of Weber and Watson:¹⁹ Man, aged fifty-eight years: Red cells, 10,000,000 per c.mm.; white cells, 8000 per c.mm.; Specific gravity, 1.066; bone-marrow, hyperplasia of the bone-marrow; red bone-marrow was where yellow marrow is normally found; spleen, tumefaction of the pulp, all organs congested; heart, left ventricle slightly hypertrophied and aortic valves have an old vegetation; some plaques in abdominal aorta; stomach, ulcer on lesser curvature.

Case of Blumenthal:² Red cells, 11,450,000; white cells, 16,300; hemoglobin, 110 per cent.; bone-marrow was hypertrophied. There were less fat cells than normal. The bone-marrow was embryonal in type because of the plethora; hypophysis, normal size; absence of chromophilic cells; spleen, enlarged, otherwise negative.

Differential count: Myelocytes, 45 per cent.; young myelocytes, 8 per cent.; specific gravity, 1.065.

Treatment. There have been many treatments recommended for this form of polycythemia: venesection, splenectomy, drugs, roentgen therapy and radium. Except in a few isolated cases no permanent cure has been found. Clinicians have been puzzled as to the proper treatment because so little is known of its pathology.

It is the purpose of this paper to give our technic in the treatment of polycythemia by the roentgen rays, and, as far as possible, our reasons for the same. At the present time we can only suggest a method which is based upon the most likely pathologic features, basing it upon what we have thought to be the probable pathology.

There are two questions that confront us: (1) The origin of the disease, and (2) the cause of the splenic enlargement. If we can assume that the disease has its origin in the bone-marrow and the lesion is a primary hyperplasia of the erythroblastic tissues, then our treatment must be of the bone-marrow, with the view of inhibiting the formation of the red cells.

So little is known of the physiology of the spleen that it is difficult to say what is the cause of the splenomegaly. Various writers have attributed the splenomegaly to tuberculosis, syphilis or to a compensatory enlargement. There is some histologic evidence that the spleen destroys erythrocytes by the phagocytic action of the cells of the spleen, and it has been suggested that these cells liberate a ferment or hemolysin which acts extracellularly. Then if the splenomegaly is a compensatory process, attempting to provide for the increased destruction of red cells, our treatment should be with a view of stimulating these functions and not destructive as hitherto used.

The treatment of the bone-marrow in polycythemia vera was first suggested by Steugel in 1907, and at the present time we feel that primarily the bone-marrow should be treated, receiving an inhibitive dose and secondarily the spleen, it receiving a stimulative dose. After we had reached our conclusions on the treatment of polycythemia it was particularly gratifying to find that Krumbhaar,⁴² in 1918, suggested that such treatment was the most rational procedure for the treatment of polycythemia vera.

Technic. The details of the technic for the treatment of polycythemia vera is very similar to that outlined by Pancoast³⁹ for the treatment of leukemia. The only exception is in the treatment of the spleen:

1. The applications are made primarily over the bones of the entire skeleton, except the bones of the head, these being omitted, due to the likelihood of the loss of the hair in this region.

2. Each area is exposed regularly and systematically, and it is recommended that the maximum dose be distributed over three successive days rather than at one time.

3. Exactness in dosage is essential because we do not wish to destroy the bone-marrow, but to inhibit the formation of the red

cells, just as in hyperthyroidism we do not wish to destroy the secreting cells of the thyroid but to inhibit their hyperactivity.

4. Frequency: Daily exposures are advocated until the series is completed. Two areas may be exposed at one time, as in polycythemia we do not get the toxemia we get in leukemia.

5. Direct exposure of the entire spleen is given after the bones of the skeleton have been completed twice, and at this time we only give a stimulative dose.

6. Duration of the treatment depends upon the individual patient. However, three series are usually required before any stability in the blood counts are noticed. After the patient has received three series he should come in at intervals for inspection and blood counts should be taken, so that any premonitory signs, such as increasing red cell counts, can be discovered early.

Comment. This report is in itself preliminary. There are many points that need further investigation: for example, whether there is an increase in hemolysis or a decrease in the formation of the red cells, or both, during roentgen ray therapy of the bone-marrow; does the function of the spleen increase after stimulative doses of the roentgen ray; does the spleen enlarge after stimulative doses of the roentgen ray?

REPORT OF CASE.—This case has been previously mentioned by Paneoust.²³

W. J. B., male, white, aged forty-two years, weaver. Admitted to University Hospital May 3, 1905. Discharged June 16, 1905.

H. P. I. Patient admitted with history of repeated hemorrhages from bowel, nose and throat, and is in a general weakened condition.

H. P. I. Illness dated back seven years, at which time he began to have pain in the lower abdomen two hours after meals. The pains were paroxysmal and relieved by taking food. For the past two years he has been having hemorrhagic diarrhea, once having as many as twenty-one stools in twenty-four hours. The diarrhea lasts for a few days. One month before admission he had two hemorrhages, one from the nose and the other from the throat, both occurring while he was asleep. Bowels are constipated and the outer portions of the movements are streaked with blood.

S. H., F. H., P. M. H. Negative except injury to the sixth and seventh cervical vertebrae when he was six years of age, at which time the patient was hanged by a rope around his neck, causing a dislocation of the sixth cervical vertebra on the seventh.

Physical Examination. Patient is of raw bony development and poor musculature. His face and hands are cyanosed at times, especially after any excitement. The superficial lymphatic glands are slightly enlarged. Arteries are soft. Pulse not rapid and of fair volume and tension. Fingers stubbed. Head negative. Eyes: Conjunctival vessels injected. Sclerae are rather muddy. Ears and nose: Normal. Mouth: Tongue dark red, otherwise normal.

Neck: Has an angular kyphosis of the sixth and seventh cervical vertebrae. Thorax: small, soft parts poorly developed. Clavicles elevated, giving rather marked fosse above and below. Respiratory movements are costo-abdominal, the chest being held very rigid, only moving slightly up and down, with very little expansion. Heart outlines: Normal. Lungs: Apices retracted, bases extending to tenth dorsal spine. Diaphragm moves very little on deep inspiration. Percussion shows slight impairment over the right apex. Everywhere else normal. Breath sounds over the right apex show harsh inspiration and prolonged expiration. Elsewhere normal. No rales heard. Dulness begins at sixth rib. Abdomen: Liver palpable half inch below costal margin. Spleen palpable two inches below costal margin. Urine: negative.

SPLenic AREA TREATED. (W. J. B.)

Year	Date.	Blood, R B C	Year.	Date.	Blood, R. B. C.
1905	May 5	9,110,000	1908	Jan. 4	7,130,000
	W. b. c., 15,360; hb., 110 per cent.; smears of blood could not be made because of the increased viscosity of the blood.			11	7,510,000
	May 10	8,880,000		18	7,333,000
	W. b. c., 8800; hb., 100 per cent.			25	7,100,000
	May 18	7,940,000		Feb. 2	6,030,000
	W. b. c., 10,800			8	8,106,000
	May 29	8,260,000		15	6,130,000
	W. b. c., 11,200.			22	6,590,000
	June 15	8,450,000		Feb. 29	6,870,000
	W. b. c., 12,960.			Mar. 8	8,020,000
	Aug. 5	8,120,000		14	6,400,000
	W. b. c., 7,970.			21	7,870,000
	Aug. 14	9,000,000		28	6,556,000
	26	8,000,000		April 4	7,480,000
	Sept. 16	7,950,000		25	7,080,000
	30*	0,800,000		May 2	7,090,000
	Oct. 7	8,200,000		9	6,940,000
	21	8,250,000		30	7,390,000
	Nov. 18	7,600,000		June 13	6,550,000
	27	8,200,000		20	7,000,000
	1906			27	7,100,000
	Jan. 1	9,220,000		July 11	6,870,000
	13	8,800,000		18	7,660,000
	27	8,800,000		Aug. 1	0,740,000
	Feb. 3	8,800,000		8	6,980,000
	10	11,000,000		12	6,600,000
	24	9,240,000		Sept. 12	7,320,000
	Mar. 3	8,800,000		26	7,400,000
	10	8,500,000		Oct. 3	7,020,000
	17	8,240,000		10	7,020,000
	24	8,160,000		17	0,300,000
	April 7	9,030,000		24	6,850,000
	28	7,720,000		31	0,350,000
	May 12	7,110,000		Nov. 7	7,630,000
	June 2	8,390,000		21	8,037,000
	9	7,420,000		Dec. 5	7,150,000
	23	9,430,000		12	6,150,000
				Dec. 19	7,360,000
				29	8,000,000

* The patient up to this time had received 240 milliamperè minutes, distance 20 inches, 4-inch spark gap. No filter.

Year.	Date.	Blood, R. B. C.	Year.	Date.	Blood, R. B. C.
1906	W. h. c., 10,320; hb.,	135 per ct.	1909	Jan. 16	7,800,000
	June 30	9,080,000		23	8,070,000
	July 7	7,960,000		30	8,300,000
	14	9,150,000		Feb. 6	8,620,000
	Aug. 4	10,200,000		13	7,590,000
	11	8,840,000		20	8,060,000
	18	9,050,000		27	6,760,000
	26	8,530,000		Mar. 3	7,180,000
	Sept. 8	7,650,000		Apr. 10	6,920,000
	15	9,450,000		17	7,320,000
	22	7,710,000		May 1	5,900,000
1907	May 25	8,250,000		8	6,620,000
Treatment of the bone marrow				13	5,680,000
was started at this time.				22	6,600,000
	June 8	8,125,000		June 19	7,490,000
	15	7,450,000		26	6,720,000
	22	7,900,000		July 3	6,150,000
	29	7,780,000		10	7,080,000
	July 6	8,800,000		17	7,090,000
	20	9,260,000		24	7,460,000
	27	9,508,000		Aug. 14	7,780,000
	Aug. 3	7,230,000		Sept. 18	7,900,000
	17	6,520,000		25	8,040,000
	31	8,500,000		Oct. 2	8,300,000
	Oct. 5	8,200,000		9	7,640,000
	17	7,760,000		16	8,250,000
	Nov. 2	7,620,000		23	9,500,000
	9	7,920,000		Dec. 4	7,030,000
	Dec. 2	7,400,000	1910	Jan. 3	7,920,000
	9	7,730,000		Mar. 28	8,250,000
	30	7,210,000			

W. h. c., 8700; hb., 120 per cent.

Treatment of the splenic area was started soon after this patient came into the hospital. After what was considered a stimulative dose the red count fell from 9,110,000 to 6,800,000 (see Table). Treatment of the spleen was continued until 1907, the red count gradually increasing, reaching as high as 10,200,000 on August 4, 1906. Stengel suggested at this time the advisability of changing the method of treatment, *i. e.*, treating the bone-marrow instead of the spleen. This was done and a more encouraging result was obtained. The red cell count decreased to 5,680,000 and the patient felt much better physically for nearly a year. The blood count did not stay down, however, and the patient gradually returned to his original condition.

REFERENCES.

1. Wakasugi, Kisaho: Zur Pathogenese der Polyzythämie, Deutsch. med. Wchnschr., Berlin, November 21, No. 47, xxxviii, 2201-2248.
2. Blumenthal, Richard: Un cas de polycythémie myélogénie, Bull. de l'acad. royale de méd. de Belgique, 1905, 4 série, 19.
3. Cabot, R. C.: A Case of Chronic Cyanosis without Discoverable Cause ending in Cerebral Hemorrhage, Boston Med. and Surg. Jour., 1899, No. 29, cxli.
4. Osler, William: Chronic Cyanosis, with Polycythemia and Enlarged Spleen: A New Clinical Entity, AM. JOUR. MED. SC., 1903, No. 2, cxxvi, 187.
5. Barker, L. F.: The Erythemias, Monographic Medicine, iii, 205-208.
6. Senator, H.: Polyzythämie und Plethora, Berlin, 1912.
7. Bence: Reference 6.
8. Lommel: Ueber Polyzythemie mit Milztumor, Deutsch. Arch. f. klin. Med., 1906, cxxvii, 315, 339.

9. Moutard-Martin et Lefas: Tuberculose primitive et massive de la rate, Bull. de la Soc. méd. des hôp. de Paris, 1899, 3e ser., p. 547.
10. Rendu et Vidal: Splénomégalie tuberculeuse sans leucémie avec hyperglobulie et cyanose, Bull. de la Soc. méd. d. hôp. de Paris, 1899, 3e ser., p. 528.
11. Nishanin: Wratschnesnaga Gaz., 1907. (Reference in Senator: Polysythämie und Plethora, Berlin, 1911.)
12. Delafield and Prudent: Text-book of Pathology, 1916.
13. Pickard, Rawson J.: Polycythemia, Jour. Am. Med. Assn., December 16, 1916, No. 25, vol. lxvii.
14. Osler, William: The Principles and Practice of Medicine, eighth edition.
15. Westenbopper: Ein Beitrag zur Pathologischen Anatomie der Plethora vera D. M. W., 1907, Nr. 36. (Reference taken from Wakasugi, bibliography.)
16. Hirschfeld, H.: Med. Klin., 1906, und Berl. klin. Wehnschr., 1907. (Reference taken from Senator, bibliography.)
17. Hirschfeld, H.: Polysythämie und Plethora, Sammlung Zwangloser Abhandlungen aus dem Gebiete der Verdauungs- und Stoffwechselkrankheiten.
18. Anders, J. M.: Chronic Polycythemia and Cyanosis, with Enlarged Spleen, AM. JOUR. MEN. SC., 1907, cxxxiii, 829-842.
19. Weber, F. P., and Watson, J. H.: Chronic Polycythemia, with Enlarged Spleen, Probably a Disease of the Bone-marrow, Internat. Clinics, 1905, No. 143, iv, 47-66.
20. Pepper, O. H. Perry: Diseases of Nutrition and Metabolism; Diseases of the Glands of Internal Secretion; Diseases of the Blood and Spleen. Reprint from Progressive Medicine, June, 1918.
21. Osler, William: Chronic Cyanosis, with Polycythemia, AM. JOUR. MED. SC., 1903, No. 2, cxxvi, 187.
22. Hurwitz, S. H., and Falconer, E. H.: The Value of Roentgen Rays and Benzene in the Treatment of Polycythemia Vera, Jour. Am. Med. Assn., No. 16, lxx, 1143-1145.
23. Swan, John M.: Polycythemia and Splenomegaly and Chronic Cyanosis, Internat. Clinics.
24. DaCosta: Leukemia and Polycythemia. Hare and Landis: Modern Treatment, 1911, vol. ii.
25. Pancoast, H. K.: Treatment of Polycythemia. Musser and Kelly: Practical Treatment, January, 1911, vol. i.
26. Staehelin, R.: Polycythemia, Berl. klin. Wehnschr., No. 3, xliiii, 101-152. Abstract, Jour. Am. Med. Assn.
27. Haldane and Smith: Jour. Physiol., 1897, xxii, 231; 1900, xxv, 331.
28. Hnatek: Reference 6, p. 34.
29. Lucas, W. S.: Erythemia or Polycythemia, with Cyanosis and Splenomegaly, Arch. Int. Med., December, 1920, No. 6, pp. 524-524. 547
30. Jones, E. Clark: Polycythemia, with Splenomegaly and Cyanosis, Lancet, No. 4607, clxxxi, 1677-1754.
31. Stadtmüller, N.: Ueber einen Fall von Erythämie, Festschrift vierzig-jährige Stiftungsfeier des deutschen Hospitals, New York.
32. Hedinus: Svenska Lab.-Sällsk. handl., 1917, xliii, 631. Abstract, Jour. Am. Med. Assn., 1918, lxx, 66.
33. Pancoast, H. K.: Experimental and Practical Application of the Roentgen Rays in Diseases of the Blood and Blood-forming Organs.
34. DeChapelle: Reference taken from 6.
35. Saunby and Russell: Reference taken from 2.
36. Türk: Reference taken from 2.
37. Bauer: Reference taken from 2.
38. Stengel, A., and Pancoast, H. K.: A New and More Rational Method of Treatment of Leukemia by the Roentgen Rays, Jour. Am. Med. Assn., April 25, 1908, i, 1317-1323.
39. Pancoast, Henry K.: Further Contributions on the Roentgen-ray Treatment of Leukemia, Am. Quart. Roent., April, 1911.
40. Stengel, A., and Pancoast, H. K.: Treatment of Leukemia and Pseudo-leukemia with Roentgen Rays, Jour. Am. Med. Assn., September 28, 1912, lxx, 1166-1169.
41. Swan, John M.: Diseases of the Blood, reprinted from New York Med. Jour. and Philadelphia Med. Jour., vol. lxxxii.
42. Pearce, R. M., Krumhaar, E. B., Frazier, G. H.: The Spleen and Anemia, 1918.